

# Vasopressin for Hemorrhagic Shock Management: Revisiting the Potential Value in Civilian and Combat Casualty Care

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**Abstract:** The evolution of trauma care is driven by a synergistic relationship between civilian and military medical systems. Although the characteristics of civilian injuries differ from those encountered on the battlefield, the pathophysiologic process of dying is the same and dominated by exsanguination and central nervous trauma. As such, therapies that interfere with the physiologic ability to compensate hemorrhage may play a key role to buy time until hemostatic surgery can be initiated. From a variety of remedies with the potential to prolong the compensation phase or to reverse the decompensation phase of shock, arginine vasopressin (AVP) is one of the most promising and best-evaluated drugs. Animal studies and various case report series provide some evidence that AVP may improve blood pressure even when conventional therapies fail, thus preventing hypovolemic cardiac arrest and enabling resuscitation from fatal hemorrhage. On the basis of this civilian experience, it seems reasonable to consider AVP for hypotensive resuscitation in the austere, resource-constrained battlefield environment. However, the significance of AVP as a rescue medication for life-threatening hemorrhage has yet to be proven.

**Key Words:** Civilian, Combat, Hemorrhage, Shock, Exsanguination, Resuscitation, Arginine vasopressin.

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Because the single major cause of death in potentially salvageable casualties is hemorrhage, recent scientific work recognizes that there is an urgent need to reconsider conventional therapies and to develop new life-support strategies.<sup>1</sup> This treatment paradigm of delayed fluid replacement or damage control resuscitation that has been established in both the civilian and military world represents a prime example for our new understanding of casualty care.<sup>2</sup> This concept perfectly addresses two major aspects of trauma care. First, trauma is predominantly a surgical disease, and out-

come is determined by the time interval between injury and surgical intervention.<sup>3</sup> As such, the potential benefit of fluid resuscitation may be abolished by the time lost in the field. Second, the negative side effects of volume replacement, namely dilution of clotting factors, boosting of hemorrhage, and induction of hypothermia are serious and potentially lethal. Based on these considerations, the current tactical combat casualty care guidelines are straight forward and target on a systolic blood pressure of 90 mm Hg or even lower, as long as the victim is still awake during casualty evacuation care.<sup>4</sup> Unfortunately, this concept has one major flaw. The key question, how to avoid cardiac arrest from exsanguination when fluid resuscitation fails and surgical intervention is not available in time, remains unanswered.

The potential role of vasopressors as first-line drugs for hemodynamic stabilization before or instead of intravenous fluids<sup>5</sup> and the appropriate rescue medication in the decompensation phase of shock is still unknown. Nevertheless, if hemodynamic stabilization could be achieved with one single injection, on-scene management would change dramatically and medics could get rid of weight relevant infusion bags. The rationale behind vasopressor drugs for cardiocirculatory stabilization in hemorrhage is based on our understanding of the physiologic response to hypovolemia; namely, pharmacologic support of physiologic, endogenous mechanisms that are involved in the compensation phase of shock and blockade of pathomechanisms that are known to cause irreversible vasoplegia.

Arginine vasopressin (AVP) is a unique endogenous hormone known even longer than epinephrine, and perhaps more important for the maintenance of homeostasis than previously thought. AVP is at least equally effective as epinephrine for resuscitation of nontraumatic cardiac arrest<sup>6</sup> and is proven to be effective in the intensive care of patients in septic shock.<sup>7–10</sup> In the physiologic response to shock, AVP is involved in multiple ways.

## Hemorrhagic Shock—A Complex Illness

Hemorrhage is the most common cause of hypovolemic shock. It leads to a fall in systemic filling pressure and venous return. The resulting decrease in cardiac minute volume and, therefore, in oxygen and nutrient supply sets off a pathophysiologic cascade (Fig. 1).<sup>11</sup> Depending on the amount of blood lost and on the organism's functional status before shock, hemorrhage can either be compensated by endogenous mechanisms or reversed by timely intervention or ends in death.

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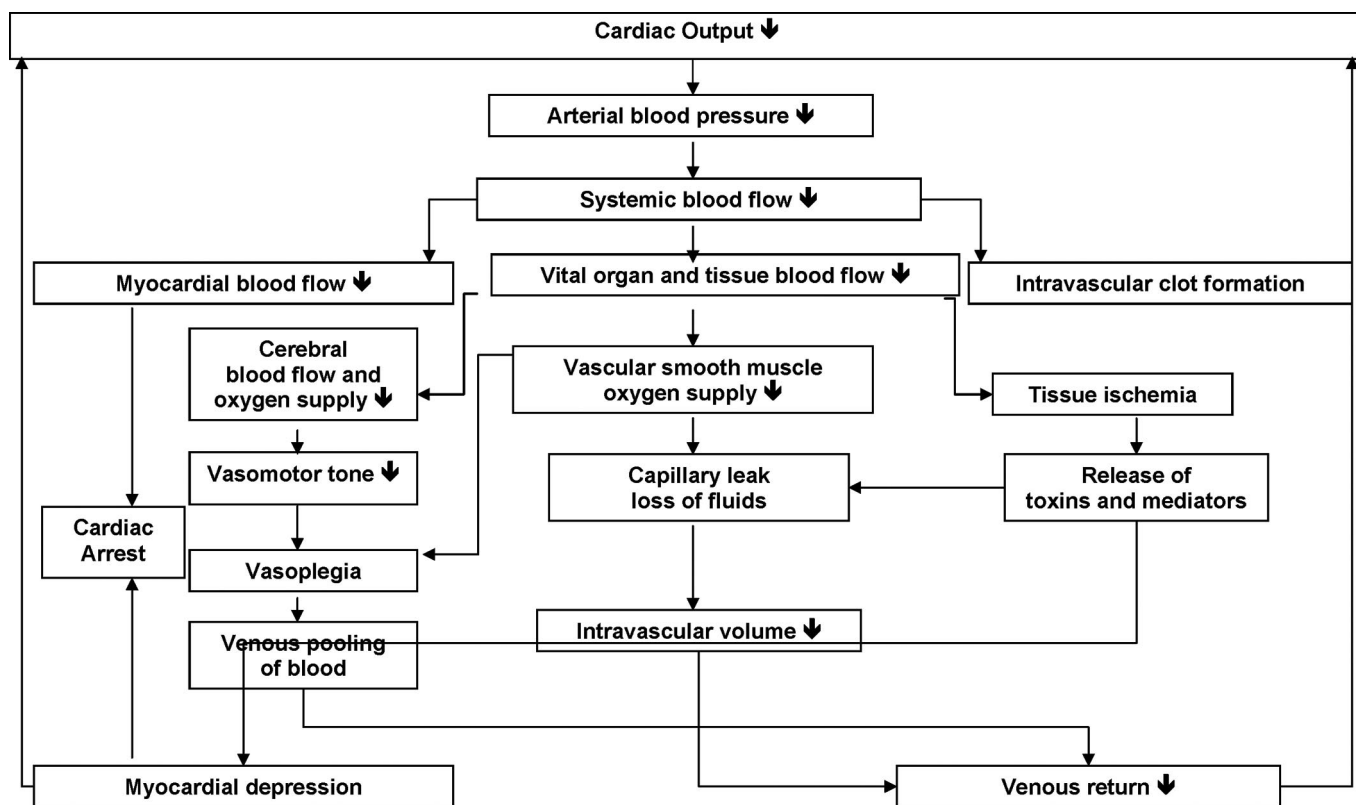
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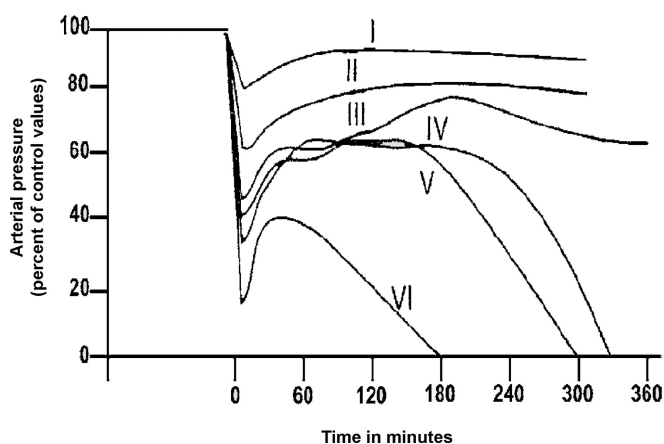
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**Figure 1.** Different types of feedback that can lead to the progression of shock (Adapted from Guyton, Textbook of Medical Physiology).<sup>11</sup>



**Figure 2.** Course of arterial pressure in dogs after different degrees of acute hemorrhage. Each curve represents the average result from six dogs (Guyton, Textbook of Medical Physiology).<sup>11</sup>

Because of feedback mechanisms, an initially compensated shock can rapidly destabilize. In principle, hemorrhagic shock is reversible provided that intravascular volume and subsequently blood pressure does not fall below a critical threshold. Once this threshold has been crossed, a brief improvement can be achieved by control of the hemorrhage, infusion therapy, and pharmacologic measures, but the bleed is nevertheless lethal (Fig. 2).<sup>11</sup>

## Mechanisms of Compensation and Decompensation During Hemorrhagic Shock

A variety of different endocrine and neurohumoral compensatory mechanisms can temporarily ensure cardiovascular stability during hypovolemia. Baroreceptor stimulation activates a sympathoadrenergic reflex that leads to the release of epinephrine from the adrenal medulla and norepinephrine from sympathetic nerve endings within 30 seconds. The vasoconstrictor effects of catecholamines are mediated via postsynaptic  $\alpha$ -1 and extrasynaptic  $\alpha$ -2 receptors. The stimulation of presynaptic  $\alpha$ -2 receptors, which occurs at the same time, blocks the continuing release of norepinephrine from nerve endings. This feedback mechanism seems to be one of the causes of the vascular decompensation seen during the late stage of hemorrhagic shock.<sup>12</sup>

AVP plays a pivotal role as an endogenous stress hormone and is significantly increased in patients with trauma.<sup>13</sup> A decrease in blood pressure induces the secretion of AVP, the levels of which can rise up to 40× physiologic concentrations, whereas at the same time there can be a 75% decrease in AVP clearance.<sup>14</sup> The importance of the secretion of AVP in humans in response to reductions in central blood volume may be underscored by the observation that maximal elevations in AVP and systemic vascular resistance are greater in individuals with high tolerance to hypovolemia compared with those with low tolerance.<sup>15</sup> This increase in AVP levels causes a rise in systemic vascular resistance (and pressure) and

a redistribution of blood, in particular to the heart, brain, and kidneys and away from skin, fatty tissue, musculature, and small bowel.<sup>16</sup> This last aspect needs to be examined more closely because prolonged bowel ischemia is thought to be one of the factors involved in the development of irreversible shock.<sup>14</sup> When hypovolemic dogs were given AVP, mesenteric blood flow decreased in relation to cardiac output, but net blood flow was significantly higher than before application of AVP because of the absolute increase in cardiac output. The main factor leading to hemodynamic stability after AVP was a rise in central venous pressure, because of volume mobilization from venous capacitance vessels to the central circulation.<sup>17,18</sup>

In an animal model of shock, Pieber et al.<sup>19</sup> found a significant decrease in angiotensin II- and norepinephrine-mediated vasoconstriction after hemorrhage of 60 minutes and 120 minutes, respectively, whereas AVP-mediated vasoconstriction was unchanged even during the late stages of shock. The authors suggested that this finding might be due to excessive nitric oxide (NO) formation during the decompensation phase of hypovolemic shock.

ATP (adenosine triphosphate)-sensitive potassium channels in vascular muscle cells also play an important role in the regulation of muscle tone and blood flow. Shock and hypovolemia lead to an increase in the activity of ATP-sensitive potassium channels, with subsequent hyperpolarization of smooth muscle cells, a decrease in calcium influx, and an increase in the formation of NO.<sup>20</sup> This mechanism is further enhanced by increased levels of atrial natriuretic peptide and accumulation of metabolic products such as H<sup>+</sup> and lactate. It is interesting to note that the vasoconstrictor action of AVP is thought to result in part from an action at this site.<sup>16,21</sup>

At a cellular level, other pathologic changes during hemorrhagic shock are the result of activation of inducible NO-synthetase, cyclooxygenase-2, and interleukin-1 $\beta$ . These changes lead to production of an excess of NO and prostaglandins, and so set off an inflammatory cascade which in turn causes a disturbance of the microcirculation that is specific to shock; with anaerobic metabolism, ATP-depletion, damage to cell membranes, vasoplegia, and erythrocyte aggregation.<sup>22</sup> AVP is again thought to play a role at the level of these mechanisms, because it has been found to inhibit the inflammatory cytokine interleukin-1 $\beta$ .<sup>16</sup>

### Modulation of Vasomotor Tone with AVP

The compensatory mechanism of the body responding to hypovolemic shock by vasoconstriction and redirection of blood flow to vital organs is one of the key factors enabling it to survive. Accordingly, it seems reasonable to consider the use of vasopressor drugs in general and of AVP in particular when hypotension becomes life threatening and endogenous plasma levels may not match the physiologic needs. As such, patients in vasodilatory septic or hemorrhagic shock have been identified to be deficient in AVP, a condition thought to be related to a defect in the baroreflex-mediated secretion of AVP and depletion of neurohypophyseal stores.<sup>23,24</sup> Interestingly, the sensitivity to exogenously administered AVP fur-

ther seems to be regulated, just as is the AVP secretion, by volume and pressure stimuli. Accordingly, in AVP-depleted subjects, even low doses of AVP yield a hypersensitive pressure response, whereas AVP has little or no effect in normal subjects or in hypotensive settings with appropriate AVP levels. This may, in part, explain conflicting findings of animal experiments on the use of AVP in hemorrhagic shock.

### Studies Advocating the Use of AVP

Morales et al.<sup>25</sup> were able to show that AVP, but neither norepinephrine nor dopamine, was able to correct hypotension during the irreversible phase of hemorrhagic shock. In this interesting animal model, prolonged hemorrhagic shock becomes refractory to conventional therapy despite volume replacement. Nevertheless, AVP resulted in stabilization of the blood pressure and survival of the animals throughout the whole duration of observations. We have developed an animal model of uncontrolled bleeding using a penetrating liver injury. Our aim was to leave the animals untreated for a short period of time (to simulate the time needed for an emergency team to arrive), then to allow a stabilization phase during which bleeding is not controlled followed by operative control of the bleed and volume therapy. A potentially fatal hypovolemia with a mean arterial pressure around 20 mm Hg developed within 30 minutes after incision into the right lobe of the liver. The point in time at which treatment began was defined by the onset of a rapidly decreasing heart rate, which is known to be a premonitory sign of prearrest bradyarrhythmia. When lactated Ringer's and hydroxyethyl starch solutions were applied at this point in time, hepatic blood loss rapidly increased. These animals died of protracted hemorrhage and dilutional anemia within 24 minutes. Animals treated with epinephrine (bolus and continuous infusion) had a brief increase in heart rate but the effect on blood pressure was only minimal. These animals died within 15 minutes. Only those animals given AVP (bolus of 0.4 IE/kg body weight followed by an infusion of 0.8 IE/kg body weight/min) had a blood pressure that was almost normal and survived for 30 minutes without further therapy. It is interesting to note that hepatic blood loss did not increase once the blood pressure increased again, possibly as a result of the temporary vasoconstriction of mesenteric blood vessels causing a decrease in portal blood flow. Animals that survived for 30 minutes under the use of AVP were managed surgically and given blood transfusions. All these animals could be extubated after a short period of weaning and were then monitored for 1 week during which none of them developed signs of organ failure.<sup>26–29</sup> In a follow-up study, animals were subjected to a mesenteric injury with uncontrolled hemorrhage stemming from the mesenteric artery. Again, pigs stabilized with exogenous AVP demonstrated reduced mortality.<sup>30</sup>

Besides the aforementioned experiments addressing abdominal hemorrhage, AVP has been shown to improve short-term survival after pulmonary contusion. Feinstein et al.<sup>31</sup> subjected anesthetized pigs to a blast to the chest, followed by either controlled arterial hemorrhage to a mean arterial pressure <30 mm Hg, or uncontrolled hemorrhage induced by partial hepatectomy. In both settings, a normal saline bolus



dose of 10 mL/kg containing 0.1 U/kg AVP followed by a continuous AVP infusion of 0.4 U/kg/h combined with normal saline significantly decreased mortality, reduced fluid requirements, and improved pulmonary function when compared with fluid resuscitation alone. In addition, the risk for bleeding was not increased when uncontrolled bleeding was stemming from the liver.

Management of patients suffering from uncontrolled hemorrhage and brain trauma is a major challenge and the concept of hypotensive resuscitation must be overruled to ensure adequate cerebral perfusion pressures (CPPs). When animals were exposed to a fluid percussion brain trauma and controlled hemorrhage, early supplemental AVP administration (0.2 U/kg bolus dose or 0.1 U/kg/h) rapidly corrected CPP, improved cerebrovascular compliance, and prevented circulatory collapse during fluid resuscitation.<sup>32</sup> Cavus et al.<sup>33</sup> addressed CPP restoration and cerebral oxygenation using the liver hemorrhage animal model. When AVP (bolus dose 0.2 U/kg followed by 0.04 U/kg/min) instead of norepinephrine (20 µg/kg followed by 1 µg/kg/min) was combined with hypertonic starch solution, CPP and cerebral oxygenation were significantly increased and restored at a faster rate.

In another recent series of experiments, Yoo et al. sought to evaluate the most appropriate dose and timing of AVP in hemorrhagic shock. Their studies demonstrated that 0.4 U/kg of AVP can be used as the most effective dose for improving the hemodynamic condition in the decompensatory phase of hemorrhagic shock. Furthermore, AVP administration before crystalloid resuscitation was found more efficient in improving hemodynamics and oxygen delivery after a prolonged hypotension phase in exsanguinated dogs. Finally, the AVP effect lasted for almost 1 hour when compared with epinephrine, which diminished after 5 minutes.<sup>5,34,35</sup>

AVP also leads to a better outcome during cardiopulmonary resuscitation (CPR) for hypovolemic cardiac arrest. Although a spontaneous circulation was also achieved with epinephrine, all the animals in the catecholamine group died within the first hour after successful resuscitation. The reasons for this are probably excessively high myocardial oxygen requirements, dramatic changes in the macro- and micro-circulation (e.g., renal perfusion stops), and subsequent acidosis. These unwanted effects were not observed with AVP.<sup>29</sup>

### AVP via the Intraosseous Route

When insertion of an intravenous catheter cannot be accomplished within appropriate time, the intraosseous access route is the alternative of first choice. Despite the fact that marrow blood flow is significantly impaired during severe hypotension, drugs and fluids will reach the systemic circulation when a pressurized infusion technique is used.<sup>36</sup> Intraosseous AVP has been shown to be effective during resuscitation from cardiac arrest.<sup>37</sup> In hemorrhagic shock, AVP decreased bone marrow blood flow to a lesser extent when compared with epinephrine.<sup>36</sup> Accordingly, AVP intraosseous AVP administration for resuscitation from hemor-

rhagic shock is feasible, particularly in the austere battlefield environment in which intravenous access may be difficult.

### Clinical Experience with AVP in Hemorrhage

At present, there are limited but positive clinical data on the use of AVP in cases of severe hemorrhagic shock and hypovolemic cardiac arrest refractory to conventional treatment.<sup>38</sup> Morales et al.<sup>25</sup> published the case histories of two patients suffering from gastrointestinal hemorrhage and shock who were resistant to conventional therapy but who responded to AVP infusions of 1 and 4 IE/kg body weight. A case of successful, albeit temporary, cardiovascular stabilization after severe trauma injuries, and cardiac arrest has also been reported by Haas et al.<sup>39</sup> Sharma and Setlur<sup>40</sup> described two cases of intraoperative hemorrhagic shock unresponsive to volume replacement and catecholamines. In both cases, AVP infusion at a rate of 0.04 U/min restored blood pressure after conventional therapies failed.

### The Vasopressin in Refractory Traumatic Hemorrhagic Shock Study

At present, an international multicenter trial, known as the Vasopressin in Refractory Traumatic Hemorrhagic Shock study, has been initiated to assess the effects of AVP versus saline placebo on hospital admission rate in adult patients of traumatic shock. Patients with systolic arterial blood pressure <90 mm Hg, who do not respond to standard shock therapy with either crystalloid, colloid, and hypertonic saline fluid resuscitation or catecholamine administration after arrival of the emergency medical service physician, will be included. The secondary endpoints of the Vasopressin in Refractory Traumatic Hemorrhagic Shock trial are hemodynamic variables, fluid resuscitation requirements, and hospital discharge rates. The experimental intervention (10 IU AVP vs. an equivalent amount of normal saline up to three times about 5 minutes apart) will be administered intravenously during ongoing standard shock treatment. The study will be launched in summer 2009 using an established network of air rescue centers.<sup>41</sup>

### A Word of Caution

Ultimately, the potential value of hemorrhagic shock treatment with AVP must be answered by long-term outcome studies. The group of patients who may ultimately benefit from this therapy could be very small and framed by individuals who may not be rescued at all or can be stabilized with conventional strategies. Data from a multicenter, prospective, cohort study designed to evaluate the outcome of blunt injured adults in hemorrhagic shock indicated that patients (1) who received early vasopressor therapy or excessive fluid resuscitation were more severely injured and had greater physiologic derangements; (2) had a twofold higher mortality when vasopressor drugs were needed within the first 24 hours postinjury; (3) had lower 24-hour survival rates when compared with fluid resuscitation only; and (4) receiving vasopressors had outcomes that were, in part, inversely related to age (younger patients receiving AVP experienced more negative outcomes than their elderly counterparts). On the basis of these data, the authors concluded that the early

use of vasopressors for hemodynamic support after hemorrhagic shock might be deleterious. Interestingly, the risk of mortality after AVP administration was not statistically significant from all vasopressor drugs analyzed.<sup>42</sup>

## CONCLUSION

On the basis of encouraging results on the use of AVP in CPR and septic shock, it seems reasonable to suggest that this therapy might provide a life-saving therapy for use in the treatment of hemorrhagic shock in combat casualties, particularly during the delay between evacuation from the battlefield to the battalion aid station or combat support hospital. Although a bolus dose of 40 IE is used during CPR and 0.04 IE/min is used in the management of septic shock, there are currently no data to identify the most effective dose for treatment of hemorrhagic shock. However, an initial bolus of 0.1 U/kg to 0.2 U/kg or 10 U seems supported by the experimental data for application in conditions of hypotensive resuscitation. Unique features of AVP include reducing or eliminating the potentially lethal effects of cardiac arrest from exsanguination and dilution of clotting factors, decreasing bleeding due to displacement of clots, and avoiding hypothermia associated with fluid replacement. Large-scale clinical investigations are still required to best determine the optimal role, dose, and timing for AVP administration in the treatment of hemorrhagic shock.

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